



TITLE:

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(Commemoration Issue Dedicated to  
Professor Tatsuo Yamamoto on the  
Occasion of his Retirement)

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## Synthesis and Complexation Stereochemistry of Crown Ethers

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Novel chiral crown ethers, which contain pinacol or biphenyl residues exerting steric effect, were synthesized from L-(+)-tartaric acid or D-(−)-mannitol as chiral sources, and the stability constants and chiral recognitions of these crown ethers were measured by use of *t*-butylammonium thiocyanate and (±)-phenylethylamine respectively.

**KEY WORDS:** Synthesis/ Complexation/ Chiral recognition/ Chiral crown ether/

The ability of cyclic polyethers to solubilize organic and inorganic cations in non-polar organic media has made these compounds available for organic syntheses and has provided a useful probe for reaction mechanism. During the last decade, a remarkable development has been brought about in this field of organic chemistry by the design and synthesis of macrocyclic molecules to mimic certain biological host-guest interactions. Cram and others have exploited the synthesis of stereospecifically functioning hosts with chiral barriers, by which "chiral recognition" between enantiomeric guest molecules has been realized.<sup>1)</sup>

Synthetic methods so far known for chiral crown ethers are based on the incorporation of D- $\psi$ -ephedrine,<sup>2)</sup> (*R*)- and (*S*)-binaphthol, D-mannitol<sup>3)</sup>, L-tartaric acid,<sup>4)</sup> (*S,S*)-cyclohexane-1,2-diol<sup>5)</sup> and others as the starting chiral source, thereby the resulting macrocycles being chiral as a whole.

It seemed of interest to undertake the design and synthesis of chiral crown ethers bearing their chirality either on the ring or in the side chain. The molecules so designed should impose a stereochemically specific environment in the neighborhood of the ring, so that they might duly be expected to make feasible an efficient chiral recognition and an asymmetric induction.

### Synthesis of Crown Ethers

Synthetic strategy is that the molecular design of ether is analyzed in chiral and structural units, and both are synthesized separately and then convergently condensed with each other to form the whole cycle. L-(+)-Tartaric acid and D-(−)-mannitol were employed as the chiral source of choice because of their easy accessibility, and pinacol and biphenyl were selected as the counterpart structural unit

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which although originally achiral, may possibly exert a steric effect on the guests. This scheme of synthesis has the following advantages: i) easy accessibility of the chiral source ii) simplicity in procedure iii)  $C_2$  symmetry and iv) convertibility into various derivatives through handles.

Di-*O*-(2-tosylethyl)pinacol **3** was derived from pinacol by the three-step transformation which involves the etherification with allyl bromide in liquid ammonia (39 % yield), ozonolysis of the allylether followed by sodium borohydride reduction to give the diol **2** (93 %), and the subsequent tosylation to yield the crystalline ditosylate **3** (59 %).

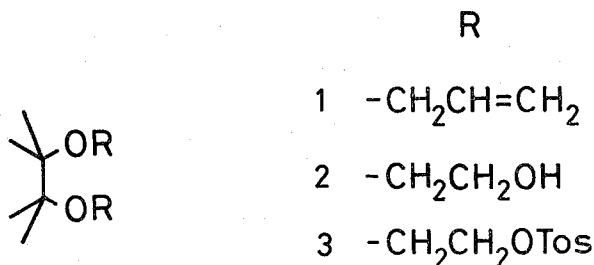


Fig. 1.

The second ditosylate **6** was obtained by the condensation of the starting 2,2'-dihydroxybiphenyl with bromoacetate to give the corresponding diester **4** (77 %), which was converted by lithium aluminum hydride reduction to the diol **5** and then tosylated to give the end product **6** (67 %).

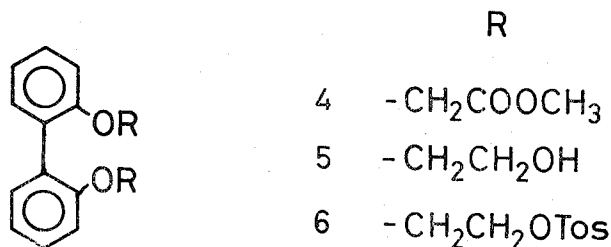


Fig. 2.

Finally, for the structural component consisting of two biphenyl residues, the synthetic scheme was successfully adopted: 2,2'-dihydroxybiphenyl was converted to the monoallylether **7** (97 %) and two equivalents of **7** were then condensed with ethylene glycol ditosylate to give the bis-allylether **8** (34 %). Attempted ozonolysis of the allyl ether **8** did not permit access to the desired diol **10**, owing to unusual degradation. Accordingly, the bis-allylether **8** was subjected to potassium permanganate oxidation under benzen/water transfer conditions with *t*-butylammonium bromide used as catalyst, which resulted in successful yield of the diacid **9** (68 %). The lithium aluminum hydride reduction of **9** to give the diol **10** (39 %), followed by tosylation in the usual manner, eventually gave the ditosylate **11** (49 %).

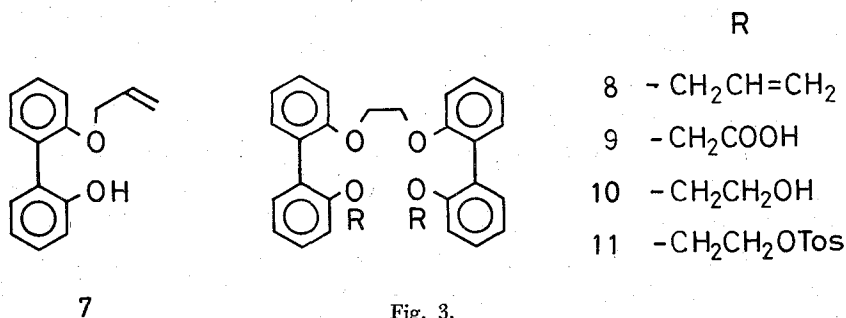


Fig. 3.

Chiral units to be incorporated in designed crown molecules were prepared starting from L-(+)-tartaric acid and D-(−)-mannitol respectively.

2,3-Bis-*O*-(2-hydroxyethyl)-1,4-di-*O*-benzyl-L-threitol **13** was prepared from L-(+)-tartaric acid according to the literature.<sup>6)</sup>

Another important key intermediate 3,4-bis-*O*-(2-hydroxyethyl)-1,2;5,6-di-*O*-isopropylidene-D-mannitol **16** was derived from D-mannitol via the isopropylidene derivative **14** (32 %) and the diallylether **15** (59 %) according to Curtis.<sup>3)</sup> Ozonolysis of **15** gave the corresponding diol **16** (48 %), whose physical properties were consistent with those in literature.<sup>3)</sup>

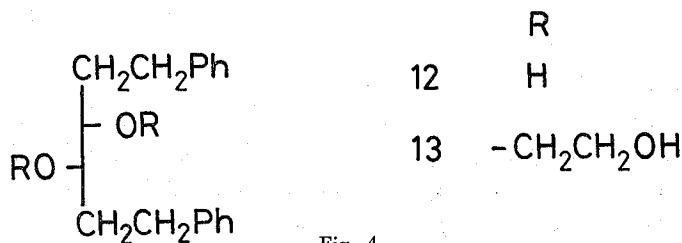


Fig. 4.

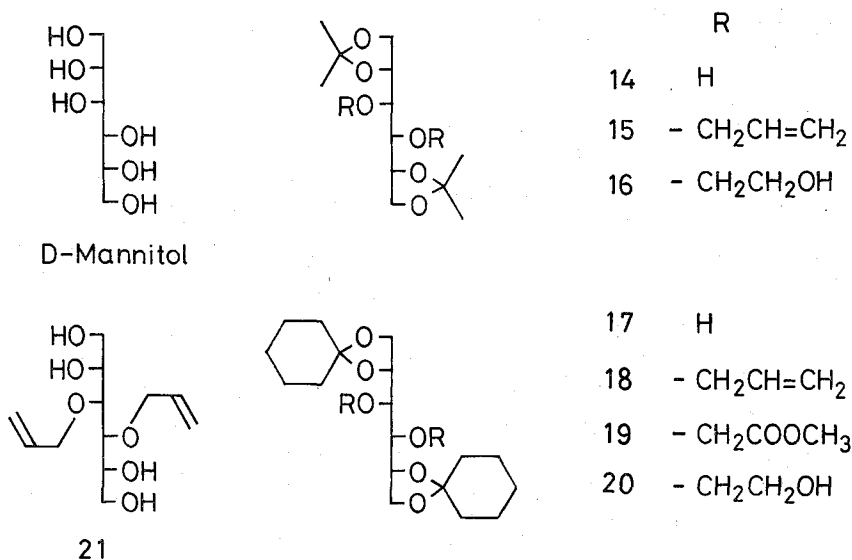


Fig. 5.

In an alternative route of transformation, 1,2;5,6-di-*O*-cyclohexylidene-D-mannitol **17** was obtained in 61 % yield by the standard method<sup>7)</sup> with cyclohexanone. Incidentally, this diol **17** is unknown in literature and the proposed structure was fully substantiated by the chemical transformations; namely, this was converted by allylation into the diallylether **18**, whose PMR-, IR-spectroscopic data and the retention time on gas chromatogram (SE 30, 1 m column) were identical in every respect with those of the same compound **18** derived from the other source, diallylether **15** by the acid-hydrolysis and the subsequent ketalization of cyclohexanone. Attempted ozonolysis of **18** failed to afford the desired cleavage product here again, so that an alternative scheme had to be adopted for a successful access to the end product; the conversion of the diol **17** by the condensation with methyl bromoacetate afforded the desired ester **19** (50 %), which in turn was reduced with lithium aluminum hydride reduction to give the desired diol **20** (45 %).

For the final convergent cyclization to form crown structure, was employed the condensation of the diol with corresponding counter ditosylate in dimethylsulfoxide at about 60°C for several days in the general procedure. Reaction parameters and physico-chemical properties for individual crowns (**25**~**31**) were given in the experimental section.

Benzylloxymethyl functionalities in the side chain permitted easy transformations or modifications to various derivatives from the parent macrocycles. Namely, dibenzyl ether **25** was hydrogenolyzed over palladium/carbon to give the diol, which was converted to the diacetate **26**.

The aza-crown ether **33** was obtained by the literature method<sup>6)</sup> and *N*-methylation of **33** afforded **34** (98 %) by the use of sodium cyanoborohydride and formaldehyde. Analogously, the benzylation of **33** resulted in the formation of *N*, *N'*-dibenzyl-aza-crown **35** (64 %). Aza-crown ether **36** was obtained (72 %) by the reaction of L-menthoxyacetyl chloride with 7,16-diaza-18-crown-6, and the reduction of **36** with diborane gave compound **37**.

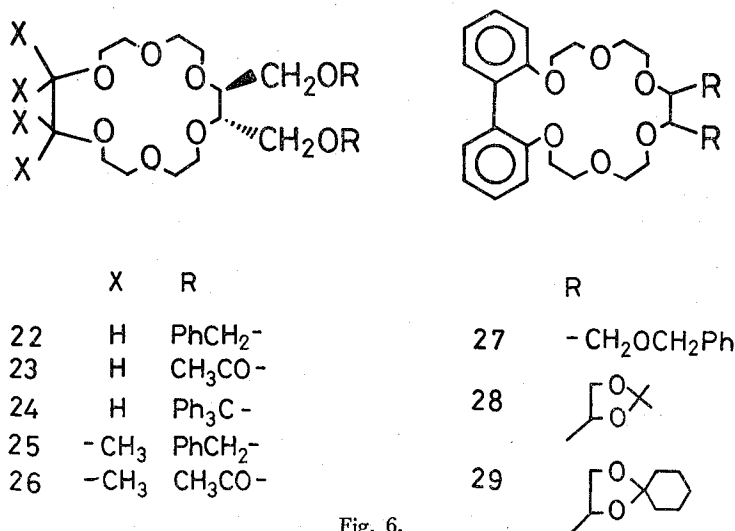


Fig. 6.

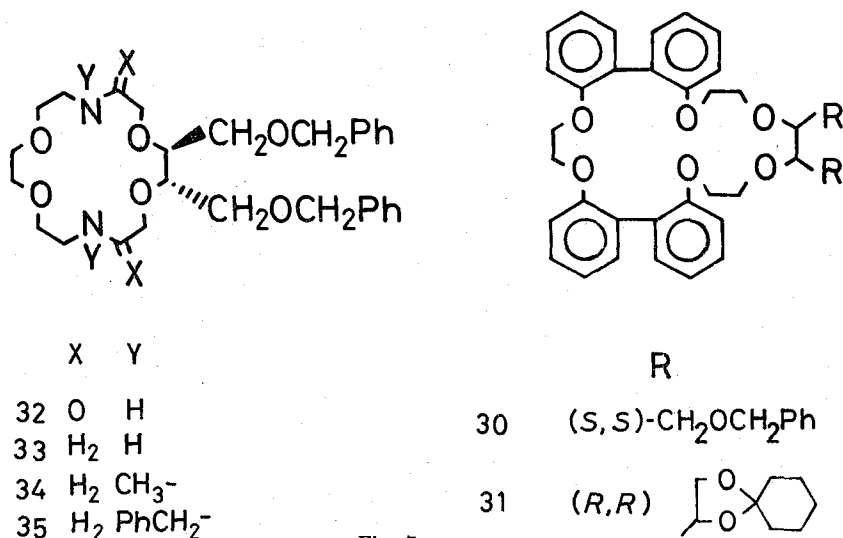


Fig. 7.

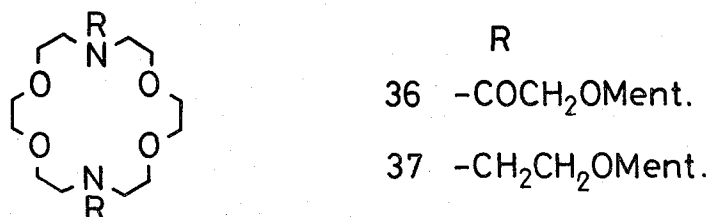


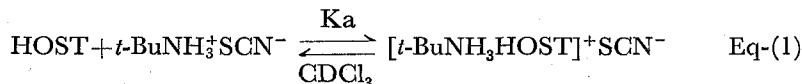
Fig. 8.

### Mechanistic Consideration of Host-Guest Complexation

The ability of macrocyclic polyethers of 18-crown-6 type to complex with primary alkylammonium salts and to effect resolution of racemic ammonium guest species has led to the development of the so-called host-guest chemistry.

Chiral recognition in the complex formation has been manifested when steric and chiral barriers were appropriately imposed by the incorporation of some pertinent bulky substituents into the polyether macromolecules. The extent of stereoselectivity in this process is a measure of the degree of complementary structural relationship between the interacting species.

From this point of view, it seemed of interest to find the correlation between the type of functional groups in the molecule and the binding properties of crown ethers, and we measured the stability constants of these crown compounds which were designed and synthesized in the present study. The measurements were made by the standard method<sup>8)</sup> with *t*-butylammonium thiocyanate in deuteriochloroform, in which the equilibrium constant  $K_a$  (L/mol) at 25°C was determined by the Cram procedure. Results obtained were summarized in Table I in comparison with those for 18-crown-6 and dicyclohexyl-18-crown-6. The association constant  $K_a$  was defined by Eq.(1) and the  $\Delta G$  values of the complex were derived from  $K_a$ .



Some interesting correlations between structure and complexing ability were found: i) These 18-crown-6 derivatives showed a superb complexing ability, *i.e.*  $3.2 \times 10^5$  for **22**,  $1.1 \times 10^5$  for **24**,  $5.2 \times 10^4$  for **23**,  $3.5 \times 10^4$  for **25**. The substitution by a pinacol residue for one ethylene unit of **22** and **25** reduced the constants by factors of 10. The conversion from benzyl ethers **22** and **25** into the corresponding acetyl derivatives **23** and **26** also diminished  $K_a$  by a factor of 6 for the first and by a factor of 20 for the second replacement. Inspection of the model reveals that steric repulsions of *t*-butyl against pinacol or acetyl groups play a significant role in these complexes.

Table I. Association Constants with *t*-Butylammonium Thiocyanate and Derived Free Energies at 25°C

Run	Scale <sup>a)</sup>	Host	$K_a$ (L/mol)	$-\Delta G$ (kcal/mol)
1	A	<b>22</b>	$3.2 \times 10^5$	7.6
2	A	<b>23</b>	$5.2 \times 10^4$	6.5
3	A	<b>24</b>	$1.1 \times 10^5$	6.9
4	C	<b>25</b>	$3.5 \times 10^4$	6.2
5	C	<b>26</b>	$1.7 \times 10^3$	4.4
6	C	<b>32</b>	— <sup>b)</sup>	—
7	A(B)	<b>33</b>	$2.2(2.7) \times 10^4$	6.0
8	B	<b>34</b>	$1.7 \times 10^5$	7.2
9	C	<b>35</b>	$1.0 \times 10^3$	4.1
10	C	<b>27</b>	$8.8 \times 10$	2.7
11	C	<b>30</b>	— <sup>b)</sup>	—
12	A	18-C-6 <sup>c)</sup>	$3.0 \times 10^6$	8.8
13	A	DCH-18-C-6 <sup>d)</sup>	$3.6 \times 10^5$	7.6

a) See ref. 8 b) The host-guest complex was not detected.

c) 18-Crown-6 d) Dicyclohexyl-18-crown-6

ii) In the complexes of aza-crown ethers, complexing ability of amine **34** compared well with that of the crown **22**. But the  $K_a$  values of **33** and **35** were lowered by factors of  $10 \sim 10^2$ . With respect to **35**, the decline may be attributed to the steric repulsion by *N*-benzyl group. On the other hand, the amide **32** failed to form the complex presumably because of the electron-withdrawing inductive effect of carbonyl function. iii) The incorporation of biphenyl segment into the ring resulted in a remarkable decrease in stability, for which the probable electron-delocalization from oxygen to aromatic systems and more certainly the steric repulsion imposed by bulky biphenyl segments are responsible.

Since the hosts as poor at complexing as **27** and **30** may possibly provide highly structured complexes, the present data suggest that a wide variety of structural units are available for designing multi-purpose crown compounds.

The resolution of guest racemate by the use of chiral crown ethers is based on the difference in stability of the formed diastereomeric complexes. In the consideration of steric influence on the stability of host-guest complex, various chiral crown ethers, synthesized from the same chiral sources so as to exert an effective steric influence, were examined for chiral recognition.

As for the experimental method, the guest phenylethylamine salt was extracted with deuteriochloroform from the deuterium oxide phase which contained the host crown ether and the guest amine in such an appropriate concentration as to form a 1:1 complex. Then, the enantiomeric excess of guest amine was estimated in deuteriochloroform. Two methods were applied for the estimation of chiral recognition. One is based on the comparison of the heights of the corresponding signals in  $^{13}\text{C}$ -NMR spectrum, caused by anisochrony for the diastereomeric complex.<sup>3)</sup> Another is the direct measurement of optical rotation of the isolated guest amine.

Experimental data (Table II) show a small extent of chiral recognition for the chiral crown ethers, but it is significant that these crown ethers derived from the same chiral source indicated the same trend of change in the extent and direction of chiral recognition. The comparison of **22** and **23** with **25** and **26** respectively revealed that the stability of the *R*-amine complex was enhanced by the incorporation of pinacol residue into the ring structure. On the contrary, the incorporation of biphenyl residue operated in the opposite direction and rather stabilized the diastereomeric *S*-amine complex by a factor of 3 as can be seen from the comparison of **22** with **27**. *S*-Amine complexes with **23** and **24**, containing bulkier group in the side chain were found to be more stable than that with **22** by a factor of 4. Likewise, the extent of chiral recognition showed the same pattern in the D-mannitol-

Table II. Chiral Recognition for Phenylethylamine

Run	Host	e.e.(%) <sup>a, b)</sup>	Config.
1	<b>22</b>	1.4	<i>S</i>
2	<b>23</b>	6.1	<i>S</i>
3	<b>24</b>	6.0	<i>S</i>
4	<b>25</b>	3.8(1.38°)	<i>R</i>
5	<b>26</b>	0.0	—
6	<b>33</b>	5.0	<i>S</i>
7	<b>34</b>	5.4	<i>S</i>
8	<b>35</b>	0.3(0.09°)	<i>R</i>
9	<b>27</b>	4.8	<i>S</i>
10	<b>28</b>	5.7(2.00°)	<i>R</i>
11	<b>29</b>	8.0(2.79°)	<i>R</i>
12	<b>30</b>	1.5(0.54°)	<i>R</i>
13	<b>31</b>	2.6(0.91°)	<i>R</i>
14	<b>36</b>	1.4(−0.48°)	<i>S</i>
15	<b>37</b>	9.0(−3.15°)	<i>S</i>

a) The value in parentheses represents the specific rotation in chloroform. b) Based on the maximum rotation of *S*-phenylethylamine,  $[\alpha]_D^{25}$  −35.2° (*c* 1.90,  $\text{CHCl}_3$ )



derived crown ethers, but the *R*-amine complexes were stable because of the opposite configuration of D-mannitol to L-tartaric acid. It is of particular interest that the *S*-amine complex turned out to be more stable apparently as the result of replacement of oxygen by nitrogen atoms in the ring, which is indicated by comparing **22** with **33**. As for the aza-crown ether series, *N*-benzylation of **33** resulted in the reversal of direction of chiral recognition. The hosts **30** and **31** involving two units of biphenyl residue were inferior to **27**, **28** and **29**, which possess one biphenyl unit.

The chiral recognition is accounted for non-rigorously in terms of steric repulsion, but this is, of course, not always the case. For example, with respect to aza-crown ether **36** and **37**, the observed data can not be explained simply by taking into account the steric, and the electronic effects may reasonably play an important role in this case.

### EXPERIMENTAL

All melting and boiling points were uncorrected. Ir spectra were recorded with a Hitachi 215 spectrometer. Pmr spectra were measured in deuterochloroform on a Varian EM-360 spectrometer. Optical rotations were observed with a Perkin-Elmer R-241. Elementary analyses were done by a Yanagimoto CHN-Corder. In pmr spectra, chemical shifts are given in  $\delta$  values relative to tetramethylsilane as an internal standard and the data are given in the order of multiplicity (s; singlet, d; doublet, t; triplet, m; multiplet), integration and assignment. In ir,  $\nu_{\max}$  are given in  $\text{cm}^{-1}$ .

**Di-O-allylpinacol 1.** Pinacol (12.0 g, 0.1 mol) was added to liquid ammonia (about 200 ml) containing metallic potassium (15.0 g, 0.38 atom), followed by dropwise addition of dry benzene (300 ml). The mixture was warmed up to room temperature in order to expel ammonia. Allyl bromide (72.6 g, 0.6 mol) was added and the mixture was stirred at room temperature overnight. The mixture was refluxed for 5 hr. Excess of metallic potassium was decomposed by adding methanol (50 ml) and the mixture was washed with water, dried over sodium sulfate and distilled to give 8.2 g of **1** (yield 39 %). bp 76–81°C/19 Torr

Ir.(film) 1640, 995 and 915( $-\text{CH}=\text{CH}_2$ ).

Pmr. 1.20(s, 12H,  $\text{CH}_3$ ), 3.87–4.07(m, 4H,  $-\text{C}=\text{CH}_2$ ), 4.87–5.40(m, 4H,  $\text{OCH}_2\text{C}$ ), 5.57–6.20(m, 2H,  $\text{C}-\text{CH}=\text{C}$ ).

$\text{C}_{12}\text{H}_{22}\text{O}_2$   $M^+$  198  
(198)

**Di-O-(2-hydroxyethyl)pinacol 2.** Ozone was bubbled through methanol solution (16 ml) containing **1** (1.6 g) under dry ice cooling with monitoring by tlc. After excess of ozone was driven by passing nitrogen stream, sodium borohydride (1.0 g) was added to the mixture. After 1 hr's stirring, 2N-hydrochloric acid (about 10 ml) was added and evaporated *in vacuo*. The product was extracted with chloroform, washed with water, dried over sodium sulfate and evaporated to give 15.5 g of **2** (yield 93 %). The product was used for the succeeding reaction without further purification.

Pmr. 1.20(s, 12H, CH<sub>3</sub>), 2.63—3.00(m, 2H, OH), 3.40—3.80 (m, 8H, OCH<sub>2</sub>CH<sub>2</sub>O).

Di-*O*-(2-tosylethyl)pinacol **3**. The titled compound was prepared by the reaction of **2** with *p*-toluenesulfonyl chloride in pyridine. yield 59 %, mp 123°C (from ethanol)

Ir.(KBr) 1360, 780 and 670 (tosyl).

Pmr. 1.03(s, 12H, CH<sub>3</sub>), 2.43(s, 6H, CH<sub>3</sub>), 3.53 and 4.03 (t J=5Hz, 8H, CH<sub>2</sub>), 7.28—7.40(d J=8Hz, 8H, phenyl).

C<sub>24</sub>H<sub>34</sub>O<sub>8</sub>S<sub>2</sub> Calcd. C; 56.01, H; 6.66

(514) Found. C; 55.36, H; 6.77

2,2'-Di(methylacethoxy)biphenyl **4**. Methyl bromoacetate (48 g, 0.31 mol) was added to the mixture of 2,2'-dihydroxybiphenyl (26.5 g, 0.14 mol) and potassium carbonate (43.2 g, 0.31 mol) in acetone (50 ml). After 21 hr's reflux, the mixture was evaporated, extracted with chloroform, washed with water, dried over sodium sulfate and evaporated *in vacuo*. The product was recrystallized from acetone to give 36.2 g of **4** (yield 77 %). mp 121°C

Ir.(KBr) 1730 and 1755(C=O).

Pmr. 4.06(s, 6H, OCH<sub>3</sub>), 4.63(s, 4H, OCH<sub>2</sub>CO), 6.80—7.53 (m, 8H, phenyl).

C<sub>18</sub>H<sub>18</sub>O<sub>6</sub> Calcd. C; 65.44, H; 5.49

(330) Found. C; 65.54, H; 5.47

2,2'-Di(hydroxyethoxy)biphenyl **5**. The diester **4** (35.1 g, 0.11 mol) in tetrahydrofuran (50 ml) was added dropwise to lithium aluminum hydride (6.1 g, 0.16 mol) in tetrahydrofuran (50 ml). The mixture was refluxed overnight and then water (6.1 ml), 15 % sodium hydroxide (6.1 ml) and water (18.3 ml) were successively added. The reaction mixture was filtered and the precipitate was washed with chloroform. The combined filtrate was evaporated to give 23.6 g of **5** (yield 89 %). The product was used in the succeeding reaction without further purification.

Ir.(film) 3350—3400(OH).

Pmr. 2.97(s, 2H, OH), 3.63 and 4.00(t J=5Hz, 8H, OCH<sub>2</sub>CH<sub>2</sub>O), 6.77—7.43(m, 8H, phenyl).

2,2'-Di(2-tosylethoxy)biphenyl **6**. The titled compound was obtained by the reaction of **5** with *p*-toluenesulfonyl chloride in pyridine. yield 67.3 %, mp 105—106°C(from benzene/*n*-hexane)

Ir.(KBr) 1360, 79 and 660(tosyl).

Pmr. 2.37(s, 6H, CH<sub>3</sub>), 4.10(s, 8H, OCH<sub>2</sub>CH<sub>2</sub>O), 6.70—7.30(m, 12H, phenyl), 7.58(d J=8Hz, 4H, phenyl).

C<sub>30</sub>H<sub>30</sub>O<sub>8</sub>S<sub>2</sub> Calcd. C; 61.84, H; 5.19

(582) Found. C; 62.11, H; 5.28

2-Allyloxy-2'-hydroxybiphenyl **7**. Allyl bromide (65 g, 0.54 mol) was added dropwise to the mixture of 2,2'-dihydroxybiphenyl (100 g, 0.54 mol) and potassium carbonate (74.2 g, 0.57 mol) in dry acetone (240 ml). After 48 hr's reflux, the mixture was washed with 10 % sodium hydroxide (450 ml) and the aqueous layer

was completely extracted with chloroform. The combined organic layer was washed with water, dried over sodium sulfate and evaporated to give 117 g of **7** (yield 97 %), which solidified in refrigerator, but melt at room temperature.

Ir.(film)	935 and 995( $-\text{CH}=\text{CH}_2$ ), 750(phenyl).
Pmr.	4.47—4.73(m, 2H, $\text{C}=\text{CH}_2$ ), 5.03—5.47(m, 2H, $\text{OCH}_2\text{C}$ ), 5.63—6.33(m, 1H, $-\text{CH}=\text{C}$ ), 6.33(s, 1H, OH), 6.80—7.50(m, 8H, phenyl).
$\text{C}_{15}\text{H}_{14}\text{O}_2$ (226)	$\text{M}^+$ 226

Bis(2-allyloxy-2'-biphenyloxy)ethane **8**. The mixture of the allylether **7** (72 g, 0.32 mol), ethyleneglycol ditosylate(50.4 g, 0.14 mol) and powdered potassium hydroxide(85 %) (19.7 g, 0.30 mol) in dry toluene (500 ml) was heated at 90°C for 20 hr, followed by another addition of powdered potassium hydroxide (19.7 g). Heating of the mixture was continued for further 24 hr and then washed with water, dried over sodium sulfate and evaporated *in vacuo*. The product was recrystallized from ethanol to give 52.2 g of **8** (yield 34 %). mp 74°C

Ir.(KBr)	930 and 1000( $\text{CH}=\text{CH}_2$ ), 750(phenyl).
Pmr.	4.07(s, 4H, $\text{OCH}_2\text{CH}_2\text{O}$ ), 4.30—4.50(m, 4H, $\text{C}=\text{CH}_2$ ), 4.87— 5.33(m, 4H, $\text{OCH}_2\text{C}$ ), 5.53—6.23(m, 2H, $\text{CH}=\text{C}$ ), 6.67—7.43 (m, 16H, phenyl).
$\text{C}_{32}\text{H}_{20}\text{O}_4$ (478)	Calcd. C; 80.31, H; 6.32 Found. C; 80.30, H; 6.22

Bis(2-acetoxy-2'-biphenyloxy)ethane **9**. The diallylether **8** (30 g, 0.063 mol) in benzene (500 ml) was added to the mixture of potassium permanganate (56.7 g, 0.376 mol) and *t*-butylammonium bromide (3.11 g, 0.01 mol) in water (800 ml) under ice cooling. The mixture was stirred at room temperature for 23 hr, followed by another addition of potassium permanganate (25 g). Stirring was continued at room temperature for 19 hr and then sodium bicarbonate (200 g) was added. The aqueous layer was separated, acidified with conc.hydrochloric acid and extracted with chloroform. The chloroform layer was washed with water, dried over sodium sulfate and evaporated to give 22.2 g of **9** (yield 68 %).

Ir.(film)	3050(broad) and 1730( $\text{COOH}$ ), 750(phenyl).
Pmr.	4.03(s, 4H, $\text{OCH}_2\text{CH}_2\text{O}$ ), 4.37(s, 4H, $\text{CH}_2\text{COO}$ ), 6.57—7.43 (m, 16H, phenyl), 8.03(br.s, 2H, $\text{COOH}$ ).
$\text{C}_{30}\text{H}_{26}\text{O}_8$ (514)	$\text{M}^+$ 514

Bis[2-(2-hydroxyethoxy)-2'-biphenyloxy]ethane **10**. The titled compound was prepared from **9** by the conventional method with lithium aluminum hydride. The product was purified by column chromatography(Wakogel C-300, benzene/ethyl acetate; 3:1 as eluent). yield 39 %.

Ir.(film)	3350(broad, OH), 750(phenyl).
Pmr.	2.60(br.s, 2H, OH), 3.60(t $J=5\text{Hz}$ , 4H, $\text{CH}_2$ ), 3.83—4.33(m, 4H, $\text{OCH}_2\text{CH}_2\text{O}$ ), 4.00(s, 4H, $\text{OCH}_2\text{CH}_2\text{O}$ ), 6.67—7.50(m, 16H, phenyl).

$C_{30}H_{30}O_6$   $M^+$  486  
(486)

Bis(2-tosylethoxy-2'-biphenyloxy)ethane **11**. The titled compound was prepared by the reaction of **10** with *p*-toluenesulfonyl chloride. The product was purified by column chromatography (Wakogel C-300, benzene/ethyl acetate; 50:1 as eluent) to give a solid matter. yield 48.6 %, mp 104–105.5°C (from ethanol).

Ir.(KBr) 1360, 780 and 735(tosyl), 750(phenyl).

Pmr. 2.37(s, 6H,  $CH_3$ ), 4.00(s, 4H,  $CH_2$ ), 4.07(br. s, 8H,  $OCH_2CH_2O$ ), 6.57–7.00(m, 20H, phenyl), 7.50(d J=8Hz, 4H, phenyl).

$C_{44}H_{42}O_{10}S_2$  Calcd. C; 66.48, H; 5.33

(794) Found. C; 66.24, H; 5.25

1,2;5,6-Di-*O*-cyclohexylidene-D-mannitol **17**. The mixture of D-(–)-mannitol (5 g, 0.027 mol) and zinc chloride (30 g, 0.22 mol) was shaken in dry cyclohexanone (150 ml) for 4 hr. After standing overnight, the mixture was poured into aqueous potassium carbonate (35 g, 0.25 mol in 35 ml) and ether (150 ml). After removal of inorganic salt, the mixture was washed with 5 % sodium hydroxide and then evaporated. The product was taken up in *n*-hexane, which on cooling separated to give 6.5 g of **17** (yield 69.1 %). mp 105–105.5°C,  $[\alpha]_D^{26}$  2.3° (*c* 2.41, MeOH).

Ir.(KBr) 3300(OH).

Pmr. 1.57(s, 20H, cyclohexylidene), 2.67(d J=7Hz, 2H, OH), 3.47–4.30(m, 8H, other protons).

$C_{18}H_{30}O_6$  Calcd. C; 63.13, H; 8.83

(342) Found. C; 62.88, H; 9.00

3,4-Di-*O*-allyl-1,2;5,6-di-*O*-cyclohexylidene-D-mannitol **18**. Allyl bromide (1.4 g, 11.6 mmol) was added to the mixture of the diol **17** (1.0 g, 2.9 mmol) and powdered potassium hydroxide (85 %) (0.77 g, 11.7 mmol). After 19 hr's heating at 90°C, the mixture was washed with water, dried over sodium sulfate and evaporated to give 1.1 g of **18** (yield 88 %). A portion of the product was purified by preparative glc (SE 30, 3/8 inch × 1 m column at 210°C) for analysis.  $[\alpha]_D^{22.5}$  15.8° (*c* 1.54,  $CHCl_3$ ).

Compound **18** from **21**. A flask equipped with a Dean-Stark column was charged with the diol **21** (11.0 g, 0.042 mol), cyclohexanone (9.84 g, 0.10 mol) and a catalytic amount of *p*-toluenesulfonic acid in benzene (255 ml). After 20 hr's reflux, the reaction mixture was cooled, washed with saturated sodium bicarbonate and water, dried over sodium sulfate and evaporated to give 11.0 g of **18** (yield 62.1 %).

Ir.(film) 1000 and 935( $CH=CH_2$ ).

Pmr. 1.57(br.s, 20H, cyclohexylidene), 3.47–4.37(m, 12H, other protons), 4.90–5.40(m, 4H,  $CH_2-C=$ ), 5.57–6.30(m, 2H,  $CH=C$ ).

3,4-Di-*O*-allyl-D mannitol **21**. The diallyl ether **15** (29 g) was hydrolyzed with 2N-hydrochloric acid (75 ml) in methanol (400 ml) at room temperature to give the solid, which was recrystallized from benzene/ethanol to give 12 g of **21** (yield 54 %). mp 109–110°C,  $[\alpha]_D^{21}$  41.7° (*c* 1.30, MeOH).

Ir.(KBr)	3450(OH), 1000 and 935(CH=CH <sub>2</sub> ).
Pmr.	3.53(br.s, 8H, other protons), 3.97–4.20(m, 4H, C=CH <sub>2</sub> ), 4.20–4.60(m, 4H, OH), 4.87–5.40(m, 4H, OCH <sub>2</sub> ), 5.57–6.23(m, 2H, CH=C).
C <sub>12</sub> H <sub>22</sub> O <sub>6</sub>	Calcd. C; 54.95, H; 8.45
(262)	Found. C; 56.02, H; 9.11

3,4-Di-*O*-(methylcarboxy methyl)-1,2;5,6-di-*O*-cyclohexylidene-D-mannitol **19**. Methyl bromoacetate (4.03 g, 26 mmol) was added to the mixture of the diol **17** (3 g, 8.7 mmol) and sodium hydroxide (0.63 g, 26 mmol) in tetrahydrofuran (50 ml) under nitrogen atmosphere. After 14 hr's reflux, the mixture was evaporated, extracted with benzene, washed with water, dried over sodium sulfate and evaporated *in vacuo*. The product was purified by column chromatography (Wakogel C-300, benzen/ethyl acetate; 20:1 as eluent) to give 2.14 g of **19** (yield 50.5 %). mp 82.5–83.0°C,  $[\alpha]_D^{27}$  11.7° (*c* 1.45, CHCl<sub>3</sub>).

Ir.(film)	1760(C=O).
Pmr.	1.57(br.s, 20H, cyclohexylidene), 3.70(s, 6H, OCH <sub>3</sub> ), 4.37(s, 4H, OCH <sub>2</sub> O), 3.70–4.37(m, 8H, other protons).
C <sub>24</sub> H <sub>38</sub> O <sub>10</sub>	Calcd. C; 59.24, H; 7.87
(486)	Found. C; 59.12, H; 7.93

3,4-Di-(2-hydroxyethyl)-1,2;5,6-di-*O*-cyclohexylidene-D-mannitol **20**. The titled compound was obtained from **19** by the conventional method with lithium aluminum hydride. The product was purified by column chromatography (Wakogel C-300, benzene/ethyl acetate; 10:1 as eluent). yield 45.2 %,  $[\alpha]_D^{27}$  6.4° (*c* 1.92, CHCl<sub>3</sub>).

Ir.(film)	3425 (OH).
Pmr.	1.60(br.s, 20H, cyclohexylidene), 2.80(br.s, 2H, OH), 3.47–4.40(m, 16H, other protons).
C <sub>22</sub> H <sub>38</sub> O <sub>8</sub>	M <sup>+</sup> 430
(430)	

1,2-Bis(benzyloxymethyl)-10,10,11,11-tetramethyl-18-crown-6 **25**. The ditosylate **3** (1.5 g, 2.9 mmol) in dimethylsulfoxide (10 ml) was added to the mixture of the diol **13** (1.2 g, 3.0 mmol) and sodium hydride (0.15 g, 6.3 mmol) in dimethylsulfoxide (20 ml) under nitrogen atmosphere. After stirring at room temperature for 6 days, the mixture was evaporated, extracted with chloroform, washed with water and dried over magnesium sulfate. The product was purified by column chromatography (aluminum oxide, benzene/ methanol; 50:1 as eluent) to give 320 mg of **25** (yield 19 %).  $[\alpha]_D^{25}$  3.3° (*c* 2.85, CHCl<sub>3</sub>).

Ir.(film)	720 and 700 (phenyl).
Pmr.	1.17(s, 12H, CH <sub>3</sub> ), 3.43–3.87(m, 22H, other protons), 4.43(s, 4H, OCH <sub>2</sub> ), 7.23(s, 10H, phenyl).
C <sub>32</sub> H <sub>48</sub> O <sub>8</sub>	M <sup>+</sup> 560
(560)	

The five crown ethers were synthesized by the same method as those for **25**, except that the reaction was conducted at 60°C.

Compound **27** from the reaction of **6** with **13**. yield 20 %,  $[\alpha]_D^{25}$  5.8° (*c* 2.55,

$\text{CHCl}_3$ ).

Ir.(film) 750 and 700(phenyl).  
 Pmr. 3.33–4.17(m, 22H, other protons), 4.43(s, 4H,  $\text{OCH}_2$ ), 7.23(s, 10H, phenyl), 6.67–7.40(m, 8H, phenyl).  
 $\text{C}_{38}\text{H}_{44}\text{O}_8$   $\text{M}^+$  628  
 (628)

Compound **28** obtained by the reaction of **6** with **16**. yield 6 %,  $[\alpha]_{\text{D}}^{23}$  12.3° (*c* 0.82,  $\text{CHCl}_3$ ).

Pmr. 1.33(br.s 12H,  $\text{CH}_3$ ), 3.17–4.10(m, 24H, other protons), 6.67–7.47(m, 8H, phenyl).  
 $\text{C}_{32}\text{H}_{44}\text{O}_{10}$   $\text{M}^+$  588  
 (588)

Compound **29** obtained by the reaction of **6** with **20**. yield 19 %,  $[\alpha]_{\text{D}}^{26.5}$  7.3° (*c* 1.89,  $\text{CHCl}_3$ ).

Ir.(film) 750(phenyl).  
 Pmr. 1.57(br.s, 20H, cyclohexylidene), 3.23–4.43(m, 24H, other protons), 6.87–7.40(m, 8H, phenyl).  
 $\text{C}_{38}\text{H}_{52}\text{O}_{10}$   $\text{M}^+$  668  
 (668)

Compound **30** obtained by the reaction of **11** with **12**. yield 11.3 %,  $[\alpha]_{\text{D}}^{28}$  3.4° (*c* 1.04,  $\text{CHCl}_3$ ).

Ir.(film) 750, 740 and 700(phenyl).  
 Pmr. 3.23–4.33(m, 14H, other protons), 4.07(s, 4H,  $\text{CH}_2\text{CH}_2$ ), 4.37 s, 4H,  $\text{OCH}_2$ ), 6.60–7.43(m, 26H, phenyl).  
 $\text{C}_{48}\text{H}_{48}\text{O}_8$   $\text{M}^+$  752  
 (752)

Compound **31** obtained by the reaction of **11** with **17**. yield 15.1 %,  $[\alpha]_{\text{D}}^{23.5}$  2.4° (*c* 2.43,  $\text{CHCl}_3$ ).

Ir.(film) 750(phenyl).  
 Pmr. 1.47(s, 20H, cyclohexylidene), 3.27–4.37(m, 20H, other protons), 6.67–7.50(m, 16H, phenyl).  
 $\text{C}_{48}\text{H}_{56}\text{O}_{10}$   $\text{M}^+$  792  
 (792)

1,2-Bis(acetoxymethyl)-10,10,11,11-tetramethyl-18-crown-6 **26** was obtained from 1,2-bis(benzyloxymethyl)-10,10,11,11-tetramethyl-18-crown-6 **25** by the hydrogenolysis and acetylation. yield 84 %,  $[\alpha]_{\text{D}}^{25}$  –14.1° (*c* 2.01,  $\text{CHCl}_3$ ).

Ir.(film) 1745( $\text{C}=\text{O}$ ).  
 Pmr. 1.17(s, 12H,  $\text{CH}_3$ ), 2.03(s, 6H,  $\text{CH}_3\text{CO}$ ), 3.77–4.37 (m, 22H, other protons).  
 $\text{C}_{22}\text{H}_{40}\text{O}_{10}$   $\text{M}^+$  464  
 (464)

*N,N'*-Dibenzyl-1,2-bis(benzyloxymethyl)-6,15-diaza-18-crown-6 **35**. The mixture of the aza-crown ether **33** (630 mg, 1.25 mmol), sodium cyanoborohydride (110 mg, 1.75 mmol), benzaldehyde (795 mg, 7.5 mmol) and molecular sieves 3A

(1 g) in methanol (10 ml) was neutralized with hydrochloric acid-saturated methanol. The mixture was stirred at room temperature for 4 days. After removal of molecular sieves and evaporation, the residue was extracted with chloroform, washed with tetramethylammonium hydroxide and water. The product was purified by column chromatography (aluminum oxide, chloroform as eluent) to give 552 mg of **35** (yield 64 %).  $[\alpha]_D^{24}$  3.7° (*c* 2.10, CHCl<sub>3</sub>).

Ir. (film) 735 and 695 (phenyl).

Pmr. 2.60–2.93(m, 8H, CH<sub>2</sub>NCH<sub>2</sub>), 3.37–3.87(m, 24H, other protons), 4.40(s, 4H, OCH<sub>2</sub>), 7.20(s, 20H, phenyl).

C<sub>42</sub>H<sub>54</sub>O<sub>6</sub>N<sub>2</sub> M<sup>+</sup> 682  
(682)

In the same manner, with formaldehyde and acetic acid in place of benzaldehyde and hydrochloric acid respectively, *N,N'*-dimethyl-1,2-bis(benzyloxymethyl)-6, 15-diaza-18-crown-6 **34** was synthesized from the aza-crown ether **33**. yield 98 %,  $[\alpha]_D^{25}$  4.9° (*c* 2.37, CHCl<sub>3</sub>).

Ir. (film) 740 and 695 (phenyl).

Pmr. 2.27(s, 6H, NCH<sub>3</sub>), 2.47–2.83(m, 8H, CH<sub>2</sub>NCH<sub>2</sub>), 3.40–3.83(m, 18H, other protons), 4.43(s, 4H, OCH<sub>2</sub>), 7.17(s, 10H, phenyl).

C<sub>30</sub>H<sub>46</sub>O<sub>6</sub>N<sub>2</sub> M<sup>+</sup> 530  
(530)

Compound **36** obtained from the reaction of L-menthoxyacetyl chloride with 7,16-diaza-18-crown-6. A solution of L-menthoxyacetyl chloride (1.95 g, 8.4 mmol) in dry benzene (10 ml) was added dropwise to a stirred solution of 7,16-diaza-18-crown-6 (1.0 g, 3.8 mmol) and triethylamine (0.92 g, 9.1 mmol) in dry benzene (20 ml) under nitrogen atmosphere. After 5 hr's stirring at 60°C, the mixture was washed with water and then dried over magnesium sulfate. The product was purified by column chromatography (Wakogel C-300, benzene/ethyl acetate as eluent) to give the solid matter, which was recrystallized from pet.ether to give 2.03 g of **36** (yield 72 %). mp 63–64°C,  $[\alpha]_D^{22}$  –64.0° (*c* 0.87, CHCl<sub>3</sub>).

Ir. (film) 1650(C=O).

Pmr. 0.63–2.50(36H, menthyl group), 3.43–3.77(m, 24H, CH<sub>2</sub>), 4.10 and 4.13 s, 4H, COCH<sub>2</sub>O).

C<sub>36</sub>H<sub>66</sub>O<sub>8</sub>N<sub>2</sub> Calcd. C; 66.02, H; 10.16, N; 4.28  
(654) Found. C; 65.83, H; 10.11, N; 4.05

Compound **37** from **36**. Diborane[from sodium borohydride (365 mg) and boron trifluoride etherate (abt. 47 %); 3.87 g] was passed into a solution of **36** (1.26 g) in dry tetrahydrofuran (10 ml) at 0°C during 1 hr. The mixture was refluxed for 2 hr and then 6N-hydrochloric acid (16 ml) was added dropwise. After 1 hr's reflux and evaporation, the mixture was made alkaline with tetramethylammonium hydroxide and extracted with chloroform. After drying over magnesium sulfate, the product was purified by column chromatography (aluminum oxide, benzene/ethyl acetate as eluent) to give 636 mg of **37** (yield 53 %).  $[\alpha]_D^{25}$  –62.3° (*c* 1.75, CHCl<sub>3</sub>).

Pmr. 0.63–2.50 (36H, menthyl group), 2.87(t J=6Hz, 8H, NCH<sub>2</sub>CH<sub>2</sub>O),

3.43–3.90(m, 24H, CH<sub>2</sub>).

C<sub>36</sub>H<sub>70</sub>O<sub>6</sub>N<sub>2</sub> M<sup>+</sup> 626  
(626)

### Chiral Recognition

In a typical run, the host compound **37** (118.3 mg, 0.189 mmol) dissolved in deuteriochloroform (1.05 ml) was shaken at 0°C with deuterium oxide (1.20 ml) containing (±)-phenylethylamine hydrochloride (175.8 mg, 1.1 mmol) and lithium hexafluorophosphate (169.8 mg, 1.1 mmol). After separation, deuteriochloroform layer was extracted with 1N-hydrochloric acid (0.75 × 4 ml) and the aqueous layer was made alkaline with aqueous ammonia. The aqueous layer was extracted with chloroform. After drying over magnesium sulfate, the volume was reduced by evaporation to 1.0 ml, in which 7.33 mg of phenylethylamine was contained as determined by gas chromatography. The extracted amine had the rotation of  $[\alpha]_D^{28} -3.15^\circ$  (*c* 0.73, CHCl<sub>3</sub>).

For the hosts **22**, **23**, **24**, **26**, **27**, **33** and **34**, the enantiomeric differentiations were deduced by the direct measurement with the deuteriochloroform phase by means of proton-decoupled <sup>13</sup>C-NMR spectroscopy. (25.00 MHz, 5 mm tube, FT conditions; acquisition time 0.68 sec, pulse width 12 μsec(90°), spectral width 5000 Hz, pulse repetition time 2.5 sec, number of data point 8192, number of transients 20000)

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